THE PRESENT SITUATION IN SYPHILIS.

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One great discovery has followed another in syphilis in the last ten years in a way that is without parallel in the history of any other disease.

First there was the demonstration by Metchnikoff and Roux in 1903 that syphilis could be produced by inoculation in chimpanzees, which was soon followed by the discovery that other apes, the rabbit, the guinea-pig, and a few other animals were susceptible to inoculation. Quick upon the heels of this basic discovery, which furnished the first opportunity for experimental study of syphilis, came the discoveries that have so greatly increased our exact knowledge of the disease.

In 1905 Schaudinn and Hoffmann ended the long search for the organism of syphilis by the discovery of the Spirochæta pallida.

At almost the same time, in 1905–6, Wassermann, Neisser, and Bruck applied the serum-complement reaction of Bordet and Gengou to the diagnosis of syphilis.

Finally, there has been the development of the arsenical chemotherapy of syphilis, begun by Uhlenhuth, and carried forward so amazingly by Ehrlich by the introduction of salvarsan in 1909.

These fundamental discoveries constitute, of course, an epoch in the history of syphilis, and it is inevitable that they should have produced a complete recasting of the methods of its management. They have in fact revolutionized not only the methods but the principles of its management, and it is to these changes in the practical management of the disease that I would direct brief critical consideration.

The great additions which have been made to the management of syphilis are:

1. Diagnosis by demonstration of the Spirochæta pallida.
2. Diagnosis by the Wassermann reaction.
3. The use of the Wassermann reaction as a criterion of the effect of treatment.
4. Diagnosis by Noguchi's cutaneous reaction.
5. Prophylaxis by inunction of 33 per cent. calomel ointment within a few hours after infection.
6. Treatment by salvarsan and its derivatives.

The Diagnosis of Syphilis by Demonstration of the Spirochæta Pallida. The presence of Spirochætæ pallidæ is the first definite proof of syphilis that can be demonstrated. They are abundant and easily demonstrable at the first appearance of the initial lesion: before the Wassermann is positive, and before there is any characteristic adenopathy or any eruption. They become less abundant as the chancre ages and somewhat less easy of demonstration, but my experience agrees with that of many others that they can be demonstrated in practically every untreated unhealed chancre. This is not the case if the lesions have been treated, for antiseptic applications, particularly mercurial applications, greatly increase the difficulty of or prevent their demonstration.

As everyone is agreed on the importance of as early a diagnosis of syphilis as possible the serious question at once arises, How distinctive are the characteristics of the Sp. pallida, and how much reliance can be placed upon the diagnosis of syphilis solely upon its demonstration? Certain spirochetes resemble more or less closely the Sp. pallida, Sp. refringens, and Sp. balanitidis found in chancres and mucous patches; Sp. buccalis and Sp. dentium in the mouth; Sp. pseudopallida in cancerous ulcers, and the Sp. pertenuis of yaws. The spirochetes most resembling Sp. pallida are Sp. dentium in carious teeth, Sp. pseudopallida, and Sp. pertenuis.

Most workers of experience believe that the Sp. pallida can be definitely distinguished from these organisms, and with that my experience agrees. But it must be emphasized that a reliable recognition of the Sp. pallida under dark field illumination or in stained specimens requires a practised careful observer who is habitually doing this particular work. Under these conditions the diagnosis of syphilis by the demonstration of Sp. pallidæ can, I believe, be reliably established. In so important a situation as the determination of syphilis in the first days of a chancre, from the recognition of Sp. pallidæ alone, I believe it is desirable to determine the character of the spirochetes by two independent observers, in order, so far as possible, to eliminate the personal equation. This I have done in numerous instances, and I have not had disagreement in the decisions.

I do not know of the unreliable work in the diagnosis of syphilis from the spirochetes as I do from the Wassermann reaction—due, I believe, to the fact that the demonstration of the organism is not commonly relied upon for diagnosis—but this is a method of diagnosis easily open to error and abuse. I do not believe the ordinary laboratory man who is not familiar by constant observation with the various spirochetes can be safely relied upon to differentiate the Sp. pallida in critical situations. The demonstration of spirochetes under dark field illumination is one of the simplest laboratory procedures, but the reliable differentiation of the Sp. pallida is not simply a matter of laboratory technique.

The demonstration of Sp. pallidæ in secondary lesions when other evidence of syphilis exists is a less critical matter. Here the demonstration is only confirmatory evidence, and it has the value of one fact in establishing the diagnosis. Occasionally this is an important fact in determining the character of confusing lesions, particularly on mucous surfaces or at mucocutaneous junctures, occurring in the course of active syphilis.

Unfortunately for diagnostic purposes the spirochetes are so few and so difficult to demonstrate in late (gummatous) lesions that their demonstration is not a practical method for establishing the character of these lesions.

THE WASSERMANN REACTION IN DIAGNOSIS. On the question of the specificity and reliability of the Wassermann reaction there is no need to waste space. The world is agreed in the affirmative upon these points. With the exception of a few now well-recognized conditions, which fortunately are not likely to lead often to confusion with syphilis, the Wassermann reaction is specific for syphilis, and can be elicited in most cases in which the disease is present. It becomes positive only when the disease has become generalized; the reaction is present, therefore, only in about 40 per cent. of cases at the appearance of the initial lesion. During the three weeks after the appearance of the initial lesion it becomes positive in about 75 per cent. of the cases, and when the cutaneous manifestations of the disease become well established, it is positive in practically all untreated cases. In late syphilis the reaction is positive in about 80 per cent. of cases. In latent cases it is positive in about 50 per cent.

In spite of the remarkable trustworthiness of the Wassermann, syphilographers generally, I believe, are conscious of many serious mistakes which are occurring in the practical application of it in diagnosis. These mistakes arrange themselves in three groups:

1. The diagnosis of syphilis from supposedly positive Wassermann's in the absence of syphilis.
2. The failure to recognize syphilis because of a negative Wassermann.
3. The reliance upon the Wassermann in conditions in which the presence or absence of syphilis has no practical bearing upon the lesion under consideration.

1. A positive finding in the absence of syphilis, of course, should not occur with a trustworthy reaction. The fact remains, however, that the mistake of reporting a positive Wassermann, when actually it does not exist and in the absence of syphilis, does occur, and, I believe, not infrequently. I have had this occur more than once in my experience in cases in which the lesions under consideration were not syphilitic, and in which Wassermann's made in my laboratory and, as a control, independently by another reliable worker, were negative.

How can such mistakes occur? Simply from the fact that the Wassermann reaction—absolutely trustworthy in itself, when positive, if correctly made and correctly interpreted—is done by human hands, and human hands are fallible. Let a laboratory man speak upon this point: "One need not emphasize the fact that in the laboratory there are no infallible methods, a fact which is most glaringly true of the Wassermann reaction. I make this statement taking for granted that the worker is experienced" (Kaplan); and then he recites for illustration a case in which from one serum three reports were obtained: a positive from a tyro; no decision from the second; negative from the third. Again: "In the Wassermann reaction the stumbling blocks are many and can be overcome by experience and practice only. The beginner makes many non-luetic sera positive, the theoretical worker does the same to a lesser extent, and the mature worker fails to report many syphilitic sera as positive."

The Wassermann reaction has many factors in it to give rise to error, and a reliable Wassermann, therefore, requires experience, careful attention to technique and to controls, and care in interpretation of results. With such requirements it is not surprising that errors occur with careless or immature workers. This is true of the original Wassermann; it is much more true, as nearly all workers are agreed, if the simplified modifications of the Wassermann are used.

2. Inaccurate work may be responsible for some negative Wassermanns in the presence of syphilitic lesions, but this mistake of reporting the Wassermann negative when it is actually positive has not been brought to my attention in the way the grosser opposite error has.

Without error in the reaction a negative Wassermann is not rare in late (tertiary) active syphilis; it occurs in 20 to 30 per cent. of the cases. Even in cases of treated active secondary syphilis one sometimes gets a negative Wassermann. It follows therefore that to rely on the Wassermann alone to make a diagnosis of syphilis is to court trouble, and this is the mistake that is constantly being made. It is not a rare experience to see a frank syphilide in the skin left unrecognized and untreated, as far as efficient treatment is concerned, because the Wassermann is negative. And if this occurs with cutaneous lesions of syphilis it surely occurs with internal lesions.

3. The third error, relying on the Wassermann in conditions which have nothing to do with syphilis, we in dermatology occasionally see. In epithelioma, especially epithelioma of the tongue, in lupus, in sycosis, in chronic eczemas of the hands, in various sorts of generalized eruptions, which surely had nothing to do with syphilis—scabies, for example—it has been my experience to see much useless puttering over Wassermanns, and in some cases, which happened actually to have syphilis, much mental perturbation because non-syphilitic lesions had not yielded to syphilitic

treatment. The syphilitic, of course, is not immune to other dermatoses; he is actually predisposed to some non-syphilitic lesions, as epithelioma of the tongue; and when one goes to giving weight to the Wassermann in non-syphilitic dermatoses in syphilitic subjects he is soon hopelessly confused.

The deduction to be made from these errors is that we should not neglect other forms of evidence. That unfortunately is the tendency whenever any laboratory test becomes available in diagnosis. I suspect there are few men, with the exception of thoroughly mature laboratory men themselves, who have not a little superstitious super-regard for laboratory findings as compared with clinical observations, when as a real fact they are more open to error and more in need of the qualities of experience and maturity of judgment than are clinical observations.

Nothing is surely more true than that the Wassermann in diagnosis must constantly be checked and compared with the clinical findings. If these are neglected, reliance upon the Wassermann must inevitably involve one in serious mistakes. As a matter of fact the lesions of syphilis upon the surface and at the orifices of the body are, as a rule, perfectly characteristic regardless of the Wassermann; and if these characteristics are neglected or not known the observer who depends upon the Wassermann will overlook one case in every five of them.

In considering the pitfalls of the Wassermann as it is practically applied no suspicion arises as to the real value of that reaction. Carried out with skill and care, and interpreted with appreciation of its limitations, a vast accumulation of experience has demonstrated it to be a perfectly trustworthy test. But it is only one fact, and its value is nearly always as confirmatory evidence of syphilis, of which there is usually abundant clinical evidence also to be found if sought with reasonable intelligence and care. It is the rarest experience to have nothing to indicate syphilis except the Wassermann, and when one hangs a diagnosis of syphilis on that evidence alone he should remember his diagnosis hangs upon a single thread of whose strength he should be perfectly certain. And even when he is certain of his positive Wassermann, if he does not know or consider his clinical conditions, the patient's trouble may still be a pus infection, or tuberculosis, or the itch, or some other non-luetic disease. The Wassermann is not a satisfactory substitute for clinical knowledge.

THE WASSERMANN AS AN INDEX OF TREATMENT. Following the great authority of Neisser, the Wassermann is being widely used as an index of the efficacy and of the necessity for treatment. Neisser's position is this: A positive Wassermann is proof of active syphilis and of the presence of living spirochetes; therefore, a positive Wassermann is an indication for specific treatment. As a corollary of this the efficacy of treatment may be judged by the effect upon the Wassermann. "Conversely a negative reaction, which means the restoration of the serum to its normal state, signifies generally if not complete destruction of the parasites at least the establishment of a condition of equilibrium between the host and the spirochetes, so that the latter assume the character of harmless saprophytes. If any treatment short of complete sterilization is to be of value it must maintain this relationship; hence the Wassermann reaction should be used to control the treatment, as it is usually the most subtle indicator of a disturbance of equilibrium with a tendency to the assumption of pathogenic activity on the part of the spirochetes." This quotation from Browning and McKenzie states well the position of those who make the Wassermann the basis for the so-called "biologic" treatment of syphilis.

It is not established beyond any possible doubt that a positive Wassermann means active syphilis. This is, however, probably true. All that can with scientific accuracy be said of a positive Wassermann is that it is evidence that the patient has had syphilis —the rest is, in part at least, assumption.

Conversely it is not established that a negative Wassermann means "the establishment of a condition of equilibrium between the host and the spirochetes, so that the latter assume the character of harmless saprophytes." On the contrary, clinical evidence proves beyond doubt that at times with a negative Wassermann the spirochetes may possess their usual virulence. All experience has shown that in 20 per cent. to 30 per cent. of cases of late active syphilis the spirochetes are showing every evidence of pathogenic activity in spite of negative Wassermann. One may even see, as I have seen, mucous patches teeming with Sp. pallidæ in late secondary syphilis with the Wassermann negative. So it is not true beyond any possible question that a positive Wassermann means active syphilis, and it is certainly not true that a negative Wassermann means a condition of equilibrium between the spirochetes and the tissues, so that the spirochetes have become harmless saprophytes.

It can be said, however, that the Wassermann reaction in syphilis is not a true specific antibody-antigen reaction. It is established that a specific syphilitic antigen is not necessary to the reaction, and a consideration of all the facts indicates that it is highly probable that the substance in the syphilitic serum that produces the specific Wassermann reaction is not true syphilitic antibody but some undetermined substance. This latter fact is exceedingly important in its practical bearing upon the question of the value of the Wassermann reaction as an index of treatment. For if it were true that the Wassermann reaction is an index of the amount of antibodies produced—in other words, of the immunity which the individual is building up to protect himself—one might well hesitate at using as an index of the efficacy of treatment what was really the index of the individual's acquired resistance to the disease. The subsidence of the Wassermann at the same time with the improvement in the condition of the syphilitic patient is one of the best evidences that it is independent of antibody and that it is a reliable index of the efficacy of treatment.

So far we are upon reasonably safe ground: the subsidence and disappearance of a positive Wassermann is an evidence of improvement in the condition of a syphilitic, and as such is an evidence in favor of the efficacy of the treatment which he is undergoing. But it is only one piece of evidence; it is not conclusive and compelling evidence that all is well; its value may be completely offset by the persistence of hyperplastic glands, by the persistence of cachexia, or, as at times may happen, the Wassermann-unheralded appearance of mucous patches or a late secondary eruption or a gumma. Its proper value then is as one symptom. It is, however, one symptom of great practical importance because it may be elicited when all others have disappeared. But as an index of the condition of a syphilitic patient or of the effect of treatment it is not entitled to preponderating consideration. It is desirable to see it disappear, as it is any other symptom of syphilis; but it is also desirable that adenopathy should subside, that mucous and cutaneous and systemic symptoms should disappear, that weight should be maintained, and that the patient's feeling of well-being should be high. If some of these evidences of the disease persist or recur we are in no position to say that the patient is better off than he would be with a persistent or recurrent positive Wassermann.

To repeat then, a negative Wassermann is an evidence of the betterment of syphilis, but it is only one form of evidence, and in weighing its importance as an index of the efficacy of treatment it is entitled to weight only in its relation to all the facts in the case.

The fact that the Wassermann is not all-important is no reason why it should not be taken at frequent intervals during treatment and given reasonable weight. And there is good reason to believe that the sooner it becomes negative and the more constantly and longer it remains negative the better is the prospect of the case, as it is with a similar course of all other symptoms of syphilis.

How long must the Wassermann remain negative before we may proclaim a patient cured? We are in no position to answer that question by any positive statement. There is now a very strong pretension that undertakes to claim a cure of syphilis after the Wassermann has remained persistently negative for a certain length of time. There is some justification for this in the abortive treatment of syphilis, when, after the chancre, neither a positive Wassermann nor any other evidence of syphilis appears. Omitting, however, these cases the clinical history of syphilis compels us to believe that we cannot give a positive assurance that the disease has gone never to return. We can give assurance after several years of a negative Wassermann, of probable immunity, as we can after several years of symptomatic freedom.

How long then shall the Wassermann be taken? If one is to be logical, as long as one's clinical judgment indicates that the syphilitic should be watched; and in my opinion that means at intervals for life. Bayly, himself a pathologist, considering the question from the theoretical standpoint, gives under what seems from the phrasing of the last half of the sentence to be logical compulsion a good answer to this question: "A single negative reaction obtained with a serum of a patient undergoing treatment by mercury or salvarsan means little but that the patient is reacting to such treatment. A series of negative results taken at intervals of three or six months after all treatment has been given up is necessary before the patient can be regarded as cured [here he seems to lose heart—W. A. P.], and even then, until twenty years have passed, we cannot be absolutely certain that the disease is completely and permanently obliterated." In other words, we are no more in position now than we have been in the past to ignore the possibility of future relapses in our luetic cases.

Space permits of only a brief consideration of the luetin reaction and the prophylaxis of syphilis by inunctions of calomel ointment, but no review of the newer syphilis can fail to mention them.

THE LUETIN REACTION. Noguchi, using a suspension of killed Sp. pallidæ, which he calls luetin, has developed a cutaneous test in syphilis analogous to the tuberculin test. It depends upon the fact that in the presence of syphilis a reaction, showing as an inflammatory nodule, appears after the injection into the skin of a drop of diluted luetin in syphilitics who are in a condition of allergy to syphilis. My experience in about two hundred cases tested with Noguchi's luetin, like that of a number of others who have used it, is that it is a valuable addition to our means of diagnosis. It has the essential quality of specificity. The reaction does not occur in other conditions than syphilis, so that with proper care in technique and interpretation it is a reliable evidence of syphilis. It can rarely be elicited in early syphilis, but in late syphilis the reaction is positive in 50 per cent. or more of the cases. And, fortunately, the reaction frequently develops in late syphilis with a negative Wassermann, so that it is a valuable supplement to the Wassermann test.

All considerations indicate that the test is a specific allergic phenomenon due to sensitization of the tissues to the virus of syphilis. The evidence for its being an indication of active syphilis is of the same character as that for the Wassermann, and as a diagnostic test and as a guide to treatment the same considerations apply to it that apply to the Wassermann. There seems good ground for believing that the luetin test will prove a useful supplement to the Wassermann in both of these functions.

THE PROPHYLAXIS OF SYPHILIS WITH CALOMEL OINTMENT. Metchnikoff and Roux announced in 1906 that syphilis can be prevented with reasonable certainty by prompt inunction of the infected point with 33 per cent. calomel ointment. Their experiments were of such great practical importance that it is surprising the subject has not created wider interest. In substance their findings are: The inunction should be made within eighteen hours at the latest; at twenty hours it fails. The ointment should be rubbed in for a few minutes; in their most critical experiment it was rubbed in for five minutes. Calomel in the proportion of one part to two of ointment is effective.

Their experiments were carried out with scientific accuracy and the strictest care for control, and the results are entitled to respect. Very extensive attempts at the prevention of syphilis based on this method have been undertaken in the United States Army and Navy, and the experience is strongly confirmatory of the value of the method. As it would appear now this very simple prophylactic procedure is one of the most important measures for the control of syphilis that has been suggested. The ointment used by Metchnikoff and Roux in their original experiments was 33⅓ per cent. calomel and 66⅔ per cent. lanoline. The ointment which they recommended is calomel 33, lanoline 67, vaseline 10. This base is stiff and it deterioates. There is no evident reason why any of the ointment bases may not be used as well, particularly benzoinated lard. The inunction should be made soon after suspected infection—within eight hours if possible; the ointment should be rubbed on to the area of suspected infection for five minutes and the surplus left on the surface.

Of course, Metchnikoff and Roux's effort was not the first attempt to prevent syphilitic infection by the use of a mercurial application. The importance of the work lies in the accurate demonstration of the effectiveness of a simple practical method of prophylaxis.

SALVARSAN IN THE TREATMENT OF SYPHILIS. The man who has to do with the treatment of syphilis has never had a greater responsibility put upon him than exists in the question of the use of salvarsan in the treatment of his cases of syphilis. The claims for it have been so strong and the sponsors for it of such high authority that it has been no easy task to exercise restraint in giving one's patients the supposed benefits of it; and yet, there are many considerations which make one hesitate at its administration in the heroic way which has been advocated and which raise serious questions concerning the sum total of its usefulness. Although the time that it has been in use is short, compared with that necessary to get any final knowledge of the ultimate value of any means of treatment in a disease so tricky as is syphilis, we are already acquiring a fund of knowledge of salvarsan that enables us more satisfactorily to determine its place in the treatment of that disease.

The questions which confront us now in considering salvarsan indicate a different situation from that which we thought we were in when salvarsan was introduced and we had the hope that in it we had an effective remedy for the cure of syphilis. Now the questions are how effective is salvarsan in syphilis? How far can it be substituted for the older means of treatment, and what are the objections to its use? It is no longer *therapia sterilizans magna*, to use one of the striking terms we learned from Ehrlich.

At present the subject of salvarsan in syphilis can be considered from two standpoints: its value as a symptomatic remedy, and its value as a curative agent. In addition we must consider its disadvantages. The disadvantages of it may be taken up first, for they have some bearing upon all considerations of its therapeutic use.

DISADVANTAGES OF SALVARSAN. Salvarsan has proved less toxic than the organic arsenic compounds of which it is the successor, but it must be at once said that it has not been found the safe remedy that it was hoped to be. It has not proved to be wholly parasitotropic and free from dangerous organotropic and neurotropic qualities, to use more of the terms for which we are indebted to Ehrlich. On the contrary it has shown again that arsenic is still treacherous, and that, combine it as we may, it is when used in quantity still dangerous. The minor disturbances from its use—fever, nausea, vomiting, diarrhea, prostration, headache, low blood pressure, temporary cardiac disturbances, transitory albuminuria and the like—may be dismissed with brief courtesy. Some of them are important as suggesting contraindications to the drug, but they are of no practical importance in so serious a problem as the cure of syphilis.

The serious accidents are in a different category. They show that salvarsan may cause death or great permanent damage of important structures. In comparison with the innumerable injections of salvarsan which have been given the deaths from it have been few, but it is true that the literature gives no adequate representation of the deaths which directly or indirectly have been due to it. And many of these deaths occur in the early stage of syphilis—the stage in which death from syphilis itself is excessively rare—and in patients who were vigorous and otherwise healthy; so that the possibility of this occurrence must be weighed in using the drug, especially in the free manner required in attempts at radical cure of the disease. Some of these deaths have been arsenical deaths, with the symptoms of arsenical poisoning, but more of them have probably been due to indirect, and in many cases not well understood, effects of salvarsan on luetic lesions in structures of vital importance. On this latter point—that the deaths are not directly due to salvarsan poisoning—much emphasis has been laid by salvarsan enthusiasts, although it would not seem a matter of great practical importance whether death is due directly to a drug or to some indirect result of the drug so long as a fatal result ensues. These salvarsan deaths make it particularly important, when vigorous use is to be made of the drug, that its contraindications be borne in mind—a fact which Ehrlich has emphasized from the start.

Of the untoward effects, those upon the nervous system are of the greatest interest and importance. They go through the whole range from the simplest to the gravest nervous disturbances—herpes, herpes zoster, multiple neuritis, paralysis, especially of cranial nerves, disturbances of memory or of orientation, epileptiform attacks. Salvarsan has not shown the affinity for the optic nerve that was such an obstacle to the use of its predecessors, notably atoxyl. Nevertheless, partial or complete optic atrophy from it has occurred numerous times. The acoustic nerve has shown greater susceptibility than the optic and involvement of it is not excessively rare. In some cases great damage both to sight and hearing has been produced. Perhaps the most extreme form of nervous involvement has been fatal cases of hemorrhagic encephalitis, of which several have occurred. Most of the nervous accidents referred to above are, there seems every reason to believe, directly due to the drug, and they show that salvarsan has the old dangerous affinity of arsenic for nerve tissue. As Busse says, these fatalities are due to the treacherous action of arsenic and the dangers are inherent in the new preparations of arsenic just as in the old; the physician must reckon with the possibility of them whenever he uses large doses of any of them.

And this raises one of the most serious questions in regard to salvarsan. Probably the greatest, and certainly the most wretched, uncontrollable dangers of syphilis are the parasyphilitic nervous affections. The nervous system bears the brunt of the untoward effects of salvarsan upon the organism. How is this to affect the parasyphilitic nervous affections? The question would be less serious if salvarsan were quickly excreted and its action on the tissues soon over. It was at first thought that this was true when salvarsan is given intravenously, but the researches of Buschke and his assistants have shown that arsenic can be recovered from the urine and blood for weeks and months, "yes, even for a year," after intravenous injection of salvarsan. And the clinical findings confirm this, for the nerve lesions of the type we are now considering may appear any time from a few days to months after the administrations of the drug.

These patients then are exposed to the danger of long-continued arsenical intoxication, and that this produces degenerative nerve changes the Manchester epidemic of chronic arsenical poisoning as well as innumerable separate experiences have shown. We have an unpleasant analogy in the effect of alcohol—another drug affecting the nervous tissues—whose persistent use is generally accepted as a predisposing cause of paresis and tabes. We are then in no position to say that this effect of salvarsan on the nervous system may not render it more susceptible to the degenerative disturbances which follow syphilis itself. Professor Buschke, of Berlin, wrote in 1912, "The theory that the intensive treatment with so neurotropic a drug, which remains so long deposited, can favor the occurrence of tabes and paresis cannot lightly be cast aside." And Professor Brocq, of Paris, wrote in January, 1913: "I do not know what it will do for the remote contingencies which we are discussing (parasyphilitic diseases, W. A. P.). We are at liberty to hope for the best, but I must admit that I am the prey of grave doubts." Only long experience can settle this important question.

The other class of nervous accidents following salvarsan are not assignable directly to its toxic effects, but occur through its effect on syphilitic lesions. These accidents may result from the sudden solution through the action of salvarsan of luetic lesions in important structures—a process that probably represents the extreme degree of the Herxheimer reaction. Others of them correspond to the usual form of Herxheimer reaction, that is, the temporary stimulation of luetic infiltrations by the drug, with the production of congestion and edema. If this occurs in meningeal lesions it may cause great temporary increase of intracranial pressure, or if in a cerebral endarteritis it may result in occlusion of the vessels. It is this reaction of active specific lesions to salvarsan—which is explained as due to the sudden liberation of supposed endotoxins—that accounts for most of the comas from salvarsan administered during the secondary period, when mild syphilitic meningeal irritation is likely to exist, and which compels caution in the use of salvarsan in the presence of syphilitic cerebral lesions.

The other form of nervous accidents following salvarsan are true syphilitic lesions in nervous tissues—the "neurorecidives" of Ehrlich, nervous lesions of syphilis, with which we were familiar before the advent of salvarsan. It was vigorously maintained until recently that these nerve involvements were not more frequent after salvarsan than before it came into use. And to support this contention the whole previous study of syphilis was indicted and charged with simply having overlooked them. Now it is admitted that they are more frequent, and this fact is taken into consideration in every scheme of salvarsan therapy. It is one of the facts which have compelled the simultaneous use of mercury. These neurorecurrences will be reverted to in considering recurrences in general.

One can, by dwelling on its dangers, exaggerate the untoward effects of salvarsan. They are relatively infrequent and, because of their infrequency, relatively unimportant in comparison with the great gain of curing syphilis if we have any reasonable assurance of attaining that end by salvarsan.

SYMPTOMATIC ACTION OF SALVARSAN. There can be no two opinions as to the specific action of salvarsan upon the active lesions of syphilis. It is a powerful symptomatic remedy. In rapidity of action it surpasses mercury or mercury and iodides in many lesions; in others, it equals or is inferior to these older remedies. In early syphilis it has a quick effect upon the initial lesion, mucous patches, and condylomas. Its action is quick upon mucous-membrane lesions generally. Its effect upon the cutaneous eruptions is not more prompt and not more complete than that of mercury. Upon the severe forms of early syphilides —large pustular eruptions, early gummatous lesions—its action is often strikingly effective. According to wide experience the effect upon the adenopathy of syphilis is surprisingly slight. Upon late gummatous lesions of the skin—apparently less upon gummas of the internal organs and upon bone lesions—the action of salvarsan is usually prompt and effective. It is in extensive and intractable lesions of this sort that it has probably its greatest field of usefulness as a symptomatic remedy; and it is the more promising here because, for the healing of such lesions, moderate doses are sufficient and the use of heroic quantities of the drug are not necessary, as in the attempts at radical cure with it. In the rare cases of severe early or late syphilis, which are not amenable to established methods of treatment, it undoubtedly is an effective addition to our means of treatment.

Aside from these latter and rare cases there is need to emphasize that salvarsan, as a rule, does nothing in gummatous lesions of syphilis that cannot be done effectively with mercury and the iodides—perhaps done slightly slower, but almost without any of the toxic dangers of salvarsan. For there is a tendency now to forget the value of the older means of treatment of these lesions. And so we constantly see reference to cases "hopeless by mercurial treatment," "intractable to mercury and iodides" or "malignant." As a matter of fact such cases, in which actual lesions of syphilis, not parasyphilis, are uncontrollable by mercury and the iodides and rational measures are excessive rarities. The treatment of such lesions by mercury and the iodides is, as a rule, one of the most definite feats of therapeutics.

As to the effect of salvarsan upon the Wassermann, evidence is conflicting. Experience in general is that except in the early primary stage it is not more effective in reversing a positive Wassermann than is mercury; in moderate doses it is less effective than safe vigorous mercurial treatment.

Curative Use of Salvarsan. What of salvarsan as a cure for syphilis—the high result that was hoped for when it was introduced? How far has it realized this hope?

In the primary stage, at the appearance of the chancre, the evidence is strong to lead us to hope that with salvarsan much more can be done than has ever been done before to abort syphilis: That is, when the syphilitic patient is seen before the disease has become generalized, while the spirochetal infection is localized around the initial lesion and before the Wassermann has become positive, it is possible in many cases to prevent the development of secondaries and hold the Wassermann negative by immediately instituting and vigorously carrying through a course of salvarsan and mercury treatment. The period of observation of these cases is still short, and success in preventing all early indications of syphilis is not conclusive proof that the patients are free from syphilis; but it is more than we can do with mercury, and it is strong presumptive evidence that the disease has been aborted.

This abortive action of salvarsan in the primary period gives it a very valuable field of usefulness. As already indicated, about 40 per cent. of cases of initial lesion, which can be distinguished by the demonstration of the Sp. pallida, show a negative Wassermann for one or two weeks after the lesion's appearance. In these cases there is a reasonable prospect that syphilis can be aborted—a prospect that justifies a vigorous attempt with salvarsan. This of course makes the early diagnosis of the initial lesion a matter of great importance.

After this brief stage of promise has passed the prospect of cure rapidly changes. It becomes less promising from week to week, and after secondaries are well established it almost or quite vanishes. That sad conclusion has been forced upon us by the accumulated evidence of recurrences in cases treated in the secondary stage. It has gradually forced the salvarsan advocates from the use of a single massive dose to courses of many repeated doses in combination with the most vigorous mercurial treatment. There the method now rests. In the opinion of salvarsan advocates some early cases can be cured by vigorous treatment. But even they admit that if cure is to be attained it is only by heroic courses of salvarsan—2 to 4 grams of salvarsan in a few weeks—combined with vigorous intramuscular use of mercury. If less than this heroic attempt at cure is made the opinion, even of some salvarsan advocates, is coming around to the view that the drug had better not be used at all. Some have gone even farther and do not use it for curative purposes after the Wassermann has become positive.

This position I believe is one which we are forced to by the logic of experience. And this position, quite aside from any hesitation about using the drug on account of its dangers, depends upon one fact—the increased frequency of severe syphilitic relapses, chiefly nervous, after the use of salvarsan. That there is an increased frequency of relapses of syphilis in the form of nervous lesions is now accepted. This is true as well, I believe, of relapses of gummatous lesions in the skin and elsewhere, but attention has been centred upon the nervous lesions because of their seriousness. Attention was early called to the frequency of nervous lesions after salvarsan by Finger, Rille, and others. The fact was bitterly denied by Ehrlich and his school, Benario, with industrious loyalty, going so far as to compile in a book the cases of nerve syphilis in the literature of presalvarsan days in order to show that their frequency is not now greater than formerly. But from that position they have been compelled to recede, and now the increased frequency of "neurorecidives" is admitted even by salvarsan enthusiasts. Thus Nichols and Hough, Nichols being one of the earliest and still one of the most enthusiastic salvarsan advocates, say: "The question still remains why these relapses are more frequent under treatment with salvarsan than with mercury."

Much difference of opinion has existed as to the reason for these relapses, some attributing them to the direct effect of the arsenic on nervous tissue, Ehrlich's school vigorously maintaining that they are lesions of syphilis. There is little doubt now that the latter view is correct, and in the reason therefore lies the strongest indictment to be made against salvarsan.

To complete the quotation from Nichols and Hough: "Some authors hold that salvarsan damages the nervous system and thus predisposes to a localization of the spirochetes in this region. It seems to us, however, that these relapses can be satisfactorily explained according to Ehrlich's ideas. In a considerable number of cases in the secondary stage the nervous system is infected with or without symptoms. . . . When such a case is treated with salvarsan the great bulk of spirochetes are suddenly destroyed. They are not simply repressed, as is the case under mercury, and the resistance of the body is not gradually stimulated against them. There remain, however, small foci of spirochetes, especially in areas which are less accessible to the circulation, such as are found in the central nervous system. After a time these spirochetes begin to multiply, and they meet no resistance such as is afforded by the continuous administration of mercury or by the natural defences of the body, because these defences have not been continuously stimulated by a large number of organisms all over the body. As a result the spirochetes which have remained grow with increased vigor and presently produce symptoms where they are located, in the nervous system." And as we would expect if this last phrase were stated in the full form logically demanded by the "increased vigor," the spirochetes, growing without the opposition of the usual resistance developed by the infected organism, cause new lesions of severer type than is usual in early syphilis.

Stated in another form this proposition is as follows: Salvarsan destroys the spirochetes except those walled off in inaccessible localities; therefore, the body is not stimulated by a general infection to the production of those antisubstances which are its natural defence, and so builds up little or no resistance. Later these isolated foci of spirochetes grow, and because of lack of acquired resistance to them grow with increased vigor, and so produce damaging lesions. Finally their growth spreads beyond the isolated focus or foci and, as after the chancre, infection becomes general, while at the same time no natural defence has been built up. In other words, the patient who is treated vigorously with salvarsan but short of absolute destruction of all the spirochetes has his day of reckoning briefly postponed, but at the price of having to meet it later under adverse conditions.

This is why the view is gaining ground that if the prospects are not good of cure from salvarsan, or if it is not to be given in the vigorous way necessary to have a chance of cure, it had better not be used at all in the early period of syphilis when the patient is building up his natural resistance.

This reasoning of course does not apply against its use as a symptomatic remedy for the treatment of the later lesions, long after the patient's specific immunity has been stimulated and utilized.

TO RECAPITULATE: 1. Salvarsan has real dangers; they are remote, but, when they occur, serious.

2. As far as can be deducted from our present knowledge there is no reason to believe that salvarsan will lessen the occurrence of parasyphilitic nervous affections, and some ground for fear that it may predispose to them, except in those cases in which it cures the disease.

3. It is a powerful symptomatic remedy.

4. In cases in which vigorous treatment is begun before the generalization of the disease there is strong ground for believing that syphilis can be aborted. This possibly applies to a few early cases with secondaries.

5. In all other cases in the secondary period its "curative" use may do more harm than good.

"Whatever be the power of the new arms which have lately been placed at our disposal for the treatment of pox, the practitioner must clearly understand that the antique rules of therapeusis have not undergone any change. He must grasp the idea that his duty is first and foremost to place the organism in the best possible state to resist and thus minimize the virulence of the infection; that by a well-ordained hygiene he may reduce to a minimum the secondary manifestations and the tertiary liabilities." (Brocq.)